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Lidocaine for Prevention of Propofol Injection-Induced Pain: A Prospective, Randomized, Double-Blind, Controlled Study of the Effect of Duration of Venous Occlusion with a Tourniquet in Adults

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ABSTRACT

BACKGROUND: Many patients experience pain on injection of propofol. The use of lidocaine to prevent propofol injection pain is common. The analgesic effect of pre-injected lidocaine has been found to increase when a tourniquet is used.

OBJECTIVE: The aim of this study was to compare the effectiveness of various venous occlusion times with lidocaine analgesia to prevent pain during propofol injection.

METHODS: In this prospective, randomized, double-blind, controlled study, women aged 18 to 45 years, classified as American Society of Anesthesiologists physical status I or II, who were scheduled to undergo elective surgery under general anesthesia induced with propofol, were randomly assigned to 1 of 5 groups: group 1, 2% lidocaine 20 mg in saline in a total volume of 10 mL and no venous occlusion; group 2, 2% lidocaine 20 mg in saline in a total volume of 10 mL plus venous occlusion for 15 seconds; group 3, 2% lidocaine plus venous occlusion for 30 seconds; group 4, 2% lidocaine plus venous occlusion for 60 seconds; and group 5, saline 10 mL and no venous occlusion. When the first 25% of the calculated propofol dose was administered, patients were asked about propofol-induced pain using a verbal pain scale (0 = no pain; 1 = mild pain; 2 = moderate pain; and 3 = severe pain). All patients and the anesthesiologist who evaluated pain severity were blinded to the study preparation being used.

RESULTS: The study comprised 100 women who were randomly divided into 5 groups of 20 patients each. Significantly more patients in group 5 (18 [90%] patients; $P < 0.05$) reported pain compared with the other treatment groups. In groups 2, 3, and 4, in which venous occlusion was applied, pain was reported during propofol injection in 6 (30%), 7 (35%), and 2 (10%) patients, respectively. The incidence of reported pain was significantly greater in group 1 (lidocaine without venous occlusion) than in group 4 ($P < 0.05$); however, the incidence of pain was similar in group 1 compared with groups 2 and 3.

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CONCLUSIONS: The present study found that pretreatment with lidocaine 20 mg with or without venous occlusion significantly reduced the incidence and the severity of pain during the injection of propofol when compared with the group with no venous occlusion administered saline. In addition, pretreatment with lidocaine 20 mg plus venous occlusion for 60 seconds significantly reduced the incidence of propofol-induced pain compared with lidocaine without venous occlusion. (*Curr Ther Res Clin Exp.* 2008;69:29–35) © 2008 Excerpta Medica Inc.

KEY WORDS: intravenous anesthetic, propofol, complication, pain, local anesthetic, lidocaine, venous occlusion.

INTRODUCTION

Propofol is widely used for induction of general anesthesia because of its fast action and recovery characteristics.[1] However, many patients experience pain on injection of this agent, and pain occurs in up to 100% of patients if a vein on the dorsum of the hand is used.[2] Several methods have been proposed to reduce the pain associated with IV administration of propofol. These include the addition of lignocaine to propofol[3]; cooling or warming the drug[4]; pretreatment with ephedrine, ondansetron, metoclopramide, opioids, thiopental, ketamine,[5] ketorolac,[6] nafamostat mesylate,[7] or acetaminophen.[8] In a recent study,[9] small doses of different formulas of propofol that included long-chain triglycerides (LCT) alone and medium-chain triglycerides (MCT) with LCT were preadministered. They found that preinjection of LCT propofol was more effective in preventing pain than LCT/MCT propofol.[9]

The use of lidocaine to prevent propofol injection pain has been extensively studied and is a common method used in clinical practice.[10] Picard and Tramèr[5] conducted a meta-analysis of 56 studies evaluating prevention of pain on injection of propofol and concluded that lidocaine should be administered with a rubber tourniquet before the propofol injection for the most effective pain prevention. It is presumed that preinjected lidocaine acts mostly as a local anesthetic. Sasaki et al[11] noted that the analgesic effect of preinjected lidocaine increased when a tourniquet was used concomitantly. A search of MEDLINE (1990–Present), using the terms *pain*, *injection*, *propofol*, *venous occlusion*, *lidocaine*, and *duration*, found limited data comparing the duration of venous occlusion needed for lidocaine to have a peripheral analgesic effect as a result of local anesthetic activity.[12] The most appropriate duration of venous occlusion in this situation needs to be determined.

The aim of this study was to compare the effectiveness of various venous occlusion times for lidocaine analgesia to prevent pain during propofol injection.

PATIENTS AND METHODS

After approval was obtained from the local ethics committee and written informed consent was obtained from the patients, women classified as American Society of Anesthesiologists physical status I or II,[12] who were aged 18 to 45 years, and who were to undergo elective gynecologic laparoscopic surgery under general anesthesia at the Dicle University Hospital, Diyarbakir, Turkey, were recruited into this prospective, random-

ized, double-blind, controlled study. Patients were excluded if they had any difficulty communicating, were uncooperative, had chronic pain, had received any type of analgesia at the site of IV cannula insertion before arriving in the operating room (including EMLA cream [AstraZeneca LP, Wilmington, Delaware], which contains lidocaine 2.5% and prilocaine 2.5%), or had a hypersensitivity reaction to anesthetic agents.

Five anesthesiologists were involved in the study in 3 steps. The first step involved one of the anesthesiologists (S.K. or S.Ö.) preparing identical syringes of saline or the study drug prior to randomization; the anesthesiologist then left the room. In the second step, a second anesthesiologist (S.T. or H.K.) performed venous occlusion with a tourniquet. For the last step, the anesthesiologist (N.B.), who evaluated pain severity during propofol injection, and the patients were blinded to the study preparation being used.

As preanesthetic medication, all patients received 150 mg of ranitidine orally 120 minutes before induction of anesthesia. On arrival in the operating room, a 20-G IV cannula was inserted into the dorsum of the nondominant hand and attached to the Ringer's solution; routine monitoring was then started. Patients were randomly assigned by computer to 1 of 5 groups: group 1, 2% lidocaine 20 mg in saline in a total volume of 10 mL and no venous occlusion; group 2, 2% lidocaine 20 mg in saline in a total volume of 10 mL plus venous occlusion for 15 seconds; group 3, 2% lidocaine plus venous occlusion for 30 seconds; group 4, 2% lidocaine plus venous occlusion for 60 seconds; and group 5 (control), saline 10 mL and no venous occlusion. The durations of tourniquet application were the same as in the study by Ewart and Whitwam.[12]

Venous occlusion was performed with a rubber tourniquet applied to the forearm ~10 cm distal to the elbow joint, which was thought to be high enough to prevent free flow of Ringer's solution. Sham venous occlusion in groups 1 and 5 was achieved using a rubber tourniquet that did not prevent the free flow of Ringer's solution. The line of Ringer's solution was closed in all groups after the rubber tourniquet was applied, and the study drug was injected over 10 seconds. The anesthesiologist responsible for the tourniquet after administration of the study drug attached the propofol injector to the vein route and then called a second anesthesiologist, whose responsibility was to carry out the injection in the operating room, and instructed the latter to start the propofol injection when appropriate.

After 25% of the calculated propofol dose of 2 mg/kg was administered (injection rate, ~1200 mL/h), the patients were asked about propofol-induced pain by an anesthesiologist (N.B.), who was blinded to the patients' group assignments, using a 4-point verbal pain scale (0 = no pain; 1 = mild pain; 2 = moderate pain; and 3 = severe pain). Thereafter, the remainder of the propofol dose was administered. Rocuronium 0.6 mg/kg was administered intravenously for muscle relaxation and to facilitate tracheal intubation, and anesthesia was maintained using sevoflurane and nitrous oxide.

STATISTICAL ANALYSIS

In the study by Fujii and Nakayama,[13] the incidence of pain during propofol injection after 1 minute of manual venous occlusion was reported to be 40% in the group administered lidocaine 20 mg. In our study, the sample size calculation was based on a

power analysis for reducing the incidence of pain from 40% to 5%. At a power of 0.8, using a significance level of $P < 0.05$, the sample size required was 20 subjects/group.

Data were analyzed using 1-way analysis of variance and the Kruskal-Wallis test. Data were expressed as mean (SD) or number (proportion), as appropriate. $P < 0.05$ was considered statistically significant. Statistical analysis was performed using SPSS for Windows, release 9.0, standard version (SPSS Inc., Chicago, Illinois).

RESULTS

The study comprised 100 women (mean [SD] age, 30.9 [7.5] years; weight, 63.9 [10.6] kg) who were randomly divided into 5 groups of 20 patients each; the 5 groups were similar in terms of demographic characteristics (**Table**).

The incidence of pain due to propofol injection in each group is shown in the **table**. Significantly more patients in group 5 (18 [90%] patients; $P < 0.05$) reported pain compared with the other treatment groups (group 1, 9 [45%] patients; group 2, 6 [30%]; group 3, 7 [35%]; group 4, 2 [10%]). In addition, significantly more patients in group 1 reported propofol-induced pain compared with group 4 ($P < 0.05$). There was no significant difference in the incidence of pain between group 4 and groups 2 or 3.

The severity of pain was significantly higher in group 5 (median pain score = 2) compared with the other 4 groups (all, median pain score = 0; $P < 0.05$). No statistically

Table. Demographic and clinical characteristics of study patients receiving propofol injection (N = 100).

Variable	Group 1 (Lidocaine) (n = 20)	Group 2 (Lidocaine + VO 15 s) (n = 20)	Group 3 (Lidocaine + VO 30 s) (n = 20)	Group 4 (Lidocaine + VO 60 s) (n = 20)	Group 5 (Saline) (n = 20)
Age, mean (SD), y	33.1 (8.8)	30.8 (6.0)	30.8 (7.3)	32.2 (9.3)	27.7 (6.1)
Weight, mean (SD), kg	67.5 (11.1)	62.2 (12.3)	63.6 (13.8)	63.4 (8.0)	62.7 (7.9)
Patients with pain, no. (%)	9 (45)*†	6 (30)†	7 (35)†	2 (10)†	18 (90)
Pain scale score,‡ median (range)	0† (0–1)	0† (0–1)	0† (0–2)	0† (0–1)	2 (0–3)
Grading of pain, no. (%)					
No	11 (55)	14 (70)	13 (65)	18 (90)	2 (10)
Mild	9 (45)	6 (30)	6 (30)	2 (10)	3 (15)
Moderate	0	0	1 (5)	0	6 (30)
Severe	0	0	0	0	9 (45)

VO = venous occlusion.
*$P < 0.05$ versus group 4.
†$P < 0.05$ versus group 5.
‡Scale: 0 = no pain; 1 = mild pain; 2 = moderate pain; 3 = severe pain.

significant differences were observed between groups 1, 2, 3, and 4 in the severity of pain.

DISCUSSION

In our study, the incidence and severity of pain were significantly less in the lidocaine groups with and without venous occlusion compared with the control group. The incidence of pain on injection of propofol after saline was 90%. In the groups with lidocaine pretreatment without venous occlusion and with venous occlusion for 15 seconds and for 30 seconds, pain on injection of propofol was not entirely controlled. The reported failure rate was between 30% and 45%. However, in group 4 (venous occlusion for 60 seconds), propofol-induced pain was reported by 10% of patients; this difference was significantly greater than in group 1 (lidocaine without venous occlusion) ($P < 0.05$), but was similar to the incidence of pain in the other 2 groups with venous occlusion (groups 2 and 3). The severity of reported pain was significantly milder in the lidocaine pretreatment groups than the control group (all, $P < 0.05$).

Pain on propofol injection is a common problem and can be distressing to the patient. The reported incidence of pain varies between 28% and 90% in adults during induction of anesthesia and may be severe.[10] The cause of pain on propofol injection is not known, although there are several proposed mechanisms. Triggering of the kinin cascade, stimulation of the nociceptive receptors at the free nerve endings located between the intima and the media layers of the venous wall, and the effect of propofol pH and concentration are all considered possible mechanisms of propofol-induced pain.[10] Preinjected lidocaine is thought to act mostly as a local anesthetic. It has been suggested that lidocaine is not effective in reducing the pain of propofol injection, except when a tourniquet is used.[11] The mechanism of action is possibly the blockade of the nerve fibers responsible for pain transmission resulting from direct irritation of the inner walls of blood vessels by propofol; this direct anesthetic effect of lidocaine is achieved when sufficient time is allowed for the drug to work.[14] However, the results of studies related to the amount of time lidocaine remains in blood vessels when a tourniquet is used are controversial.[12] Local anesthetic activity of lidocaine may be high due to long duration, but in the study of Ewart and Whitwam,[12] lidocaine was most effective at reducing pain when administered immediately before applying propofol.

Liaw et al[15] found that IV lidocaine was retained in the veins for 1 minute, and injecting propofol after releasing the rubber tourniquet was found to be effective in reducing pain when compared with the saline group. In this study, 3 different techniques for reducing propofol injection pain with metoclopramide were compared with lidocaine or saline to evaluate the most effective method in reducing propofol injection pain.[15] The study differed from ours in that lidocaine 40 mg was used; we used lidocaine 20 mg. Liaw et al found the incidence of pain to be 11% in 35 patients. Ewart and Whitwam[12] found that the incidence of pain increased as the time increased between the injection of lidocaine and propofol, based on observing 5 randomly selected groups of 20 unpremedicated patients scheduled for minor gynecologic surgery. A tourniquet was applied to the proximal part of the forearm and a 23-G cannula was placed in a vein in the dorsum of the hand. In the control group,

the tourniquet was released; in the other groups, lidocaine was injected, producing a "mini-Bier block." After intervals of 10, 30, 60, or 90 seconds, the tourniquet was released and propofol was administered. Pain was significantly reduced in the groups to which lidocaine was administered after 10 or 30 seconds of venous occlusion before propofol administration ($P < 0.05$ and $P < 0.01$, respectively). The authors suggested that lidocaine was most effective in reducing pain when administered immediately before propofol injection and that there was no difference in the frequency of pain after injections of propofol between groups with venous occlusion for 60 and 90 seconds and the control group.[12]

Venous occlusion was carried out with a rubber tourniquet for 2 minutes in a study by Fujii and Nakayama.[2] They used 2% lidocaine 20 mg and added 0.9% normal saline to make a total volume of 6 mL. The authors found that lidocaine pretreatment with venous occlusion for 2 minutes significantly reduced the incidence of propofol-induced pain from 90% to 27% ($P < 0.01$). In another study by Fujii and Nakayama,[13] a rubber tourniquet was applied for venous occlusion and 1% lidocaine 20 mg was administered with saline to make a total volume of 2 mL. After 1 minute, the tourniquet was released and propofol was injected. This study found that lidocaine 20 mg with venous occlusion for 1 minute prevented pain on propofol injection in 12 of 30 patients (40%). The findings in our study were not comparable to the findings of these studies. We think that the higher total volume used in our study (10 mL) increased the distribution of the drug, leading to a good local anesthetic effect that varied with the residence time of the drug.

When the local anesthetic was administered intravenously after venous occlusion using the rubber tourniquet method, the total volume of the drug dose affected drug distribution. Although the dose of lidocaine used in these studies was the same dose we used, the total volume administered was lower than the volume we used. Lidocaine has been used most frequently for regional IV anesthesia at concentrations of 0.25% to 0.5%.[16] In our study, lidocaine was used as 20 mg (2% mL) in a total of 10 mL of solution (0.2%), resulting in better distribution and greater analgesia from lidocaine during venous occlusion. Lidocaine 20 mg plus venous occlusion of varying durations was associated with a significantly greater reduction in propofol-induced pain compared with the lidocaine without venous occlusion group and the saline group. This effect might have been due to the higher total volume of the injected solution than that in the other studies mentioned above.

One challenging factor was the difficulty ensuring that the study was randomized and double-blind with regard to tourniquet application. The anesthesiologist who evaluated the patients was kept waiting outside of the operating room during the preparation stage, so that he was blinded to whether or not venous occlusion was performed. The anesthesiologist who prepared the study drug left the operating room during the other stages of the study so that the anesthesiologist performing the venous occlusion did not know whether the drug being administered was saline or lidocaine. In addition, the patients did not know which drugs they were receiving or whether or not the tourniquet was a sham. When all of these procedures are taken into consideration, we believe that we were able to ensure the study was randomized and double-blind.

CONCLUSIONS

The present study found that pretreatment with lidocaine 20 mg with or without venous occlusion significantly reduced the incidence and the severity of pain during the injection of propofol when compared with the control group administered saline without venous occlusion. In addition, the incidence of pain was significantly lower in the group administered lidocaine plus venous occlusion for 60 seconds compared with the group administered lidocaine without venous occlusion.

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